Class IV Laser therapy on Ejection Fraction, Cardiac Biomarkers and Functional Outcomes among individuals with Acute Coronary Syndrome

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SYNOPSIS SUBMITTED

To

Maharishi Markandeshwar (Deemed to be University)

Mullana, Haryana, India

In partial fulfillment of the requirements for the degree

Doctor of Philosophy

(Physiotherapy)

SUBMITTED

By

Mandeep Kumar Jangra

Roll No: 1820745

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Certificate

This is to certify that the PhD thesis synopsis / protocol on, **"Class IV laser therapy on Ejection Fraction, Cardio Biomarkers and functional outcomes among individuals with Acute Coronary Syndrome"** has been done by **Mandeep Kumar Jangra** under our supervision. We are satisfied with the work presented by the candidate towards the partial fulfillment of Doctor of Philosophy (PhD) in Physiotherapy. This is an original work submitted only to Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana and is free of any plagiarism at the time of his submission.

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Abstract

Background: Cardiovascular disease is a broad term which included the disease of heart and blood vessels and a major cause of mortality worldwide. Coronary heart disease (CHD), coronary artery disease (CAD) and acute coronary syndrome (ACS) are some clinical conditions which lead to ischemic heart disease. ACS is a major health issue which reaches epidemic proportion and is a single and foremost cause of deaths and Disability Adjusted Life Years (DALYs) which accounts for approximately 7 million deaths and 129 million DALYs annually. According to Global Burden of Disease study, Overall death rate due to CVD (272/100000) in India is higher than the global (235/100000).

Aim: To determine the efficacy of Class IV Laser therapy in improving ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome.

Method: In this pre-test post-test randomized sham controlled trial, pre intervention base line assessment of left ventricular ejection fraction, CK-MB, Troponin-I, SAQ, size of myocardial infarction will be done. The experimental group will subject to irradiated with Class IV laser therapy along with the standard treatment regime; immediately after the angioplasty and subsequent two days and sham controlled group will subject to irradiation but the equipment will be kept off (placebo). On the 3rd day post intervention, repeated measurement of outcome measures will be made.

Discussion: Laser therapy have anti-inflammatory effect, improves microcirculation, cardioprotective effects, so class IV laser may be an effective tool to reduce myocardial reperfusion injury and improve functional outcomes among the individuals with acute coronary syndrome.

Key words: Class IV Laser, Laser Therapy, Acute Coronary Syndrome, Ejection Fraction, Cardiac Biomarker.

1. Introduction

Cardiovascular disease is a broad term which included the disease of heart and blood vessels and a major cause of mortality worldwide.[1] Stroke and Ischemic heart disease are the most common cause of death among cardiovascular diseases.[2] Coronary heart disease (CHD), coronary artery disease (CAD) and acute coronary syndrome (ACS) are some clinical conditions which lead to ischemic heart disease. Usually, healthcare professionals use CAD, CHD and ACS interchangeably, but actually they are not the same. CHD occurs due to CAD, while ACS is a subcategory of CAD. CAD is characterized by obstruction in coronary blood flow due to atherosclerotic changes in coronary arteries which can be asymptomatic, while ACS always present with a symptom includes unstable angina or myocardial infarction.[3] CHD/IHD includes the differential diagnosis of acute coronary syndrome, silent myocardial ischemia.[4]

ACS is a major health issue which reaches epidemic proportion and is a single and foremost cause of deaths and Disability Adjusted Life Years (DALYs) which accounts for approximately 7 million deaths and 129 million DALYs annually.[4,5] The incidence of CAD is decreasing in developed countries; prevalence will not reduce due to immigration and progressive population aging.[6] In India, CVD accounts for one fourth of all mortality.[7] IHD and stroke are the most common cause and account for more than 80% of the mortality due to CVD. Overall death rate due to CVD (272/100000) in India is higher than the global death rate (235/100000) as stated by the Global Burden of Disease study and premature mortality due to CVD increased by 59% from 1990 to 2010. Prevalence of IHD increases tremendously in both rural and urban India, it was 2% among urban population in 1960 which rises 7 times upto 14% by 2013 and 1.7% to 7.4% among rural population.[2,8,9] In 2005, The Macroeconomic Commission for Health stated that number of IHD patients in India will increase 359 lakh in 2005 to 615 lakh in 2015.[10] A cohort

study in Mumbai revealed that CVD equally affects the individuals with high and low socioeconomic status.[11] A CREATE registry reported that outcomes after ACS were worse in low socioeconomic status.[12] On the other hand, one study demonstrated that under-diagnosis and under-reporting of CVD are more common among the low socio economics status.[13]

Acute coronary syndrome is an umbrella term which encircles a range of thrombotic coronary artery disease and refers to a group of clinical symptoms which represent acute myocardial ischemia as a common end result; it includes unstable angina (UA), ST segment elevation myocardial infarction (STEMI), Non-ST segment elevation myocardial infarction (NSTEMI).[14-18] UA and NSTEMI are similar in clinical presentation as well as pathophysiological origin but their severity is different. NSTEMI can be diagnosed when ischemia to myocardium is sufficient to cause a myocardial damage. When there is any damage to myocardium, the biomarkers (CK-MB, Troponin I&T) of myocardial necrosis release in the circulation. It is considered as unstable angina if there is no elevation in the biomarker level within hours of initial onset of symptoms.[14] The term Myocardial Infarction (MI) is used when myocardial necrosis occurs.[19] Individuals with suspected acute coronary symptoms are important population in the triage, which requires immediate action and appropriate diagnosis. In the past decades, diagnostic and therapeutic pathways for acute coronary syndrome improve significantly which include a faster and accurate diagnostic algorithm based on the cardiac biomarkers.[20] Approximately 2/3rd cases of ACS are of N-STEMI and 1/3rd are of STEMI.[17]

The clinical presentation of ACS is broader from chest pain, cardiac arrest, sweating, breathlessness, electrical or haemodynamic instability with cardiogenic shock due to ongoing ischemia.[21] Persistent ischemia leads to death of cardiomyocyte/ cardiomyocyte necrosis. Myocardial infarction can occur during the natural course of an atherosclerosis of coronary

artery.[22,23] Left ventricular function is a powerful and independent indicator of clinical outcomes followed by any myocardial injury and recommended as class I practice guideline by ACC and AHA. Decreased LVEF increase the rate of mortality as well as chances of sudden cardiac death.[24,25] Following ACS, left ventricular ejection fraction is recommended to define prognosis and intervention. Guidelines by ACC/AHA for ST-Elevated Myocardial Infarction (ACC/AHA STEMI) suggests that contrast left ventriculography to be done at the time of cardiac catheterization and transthoracic echocardiography (TTE) should be performed on the second/third post admission day for cases in which mechanical complications are suspected. In patients with moderate to severe LV dysfunction, a reassessment of LV function at least 40 days later is strongly recommended to guide the need for device-based therapy.[26]

Due to decreased left ventricular function the overall quality of life is also affected adversely. Quality of life can be assessed by self-administrated questionnaire; a number of questionnaires are available to assess health related quality of life among individuals with cardiac disease like EQ-5D, WHOQOL, HeartQOL, Seattle Angina Questionnaire (SAQ), SF-36.

Early risk stratification in the initial hours of patient reporting helps in determining prognosis and to decide whether a patient should be managed either conservatively or an early invasive intervention is needed. As well as it also helps to determine the pharmacologic therapies.[16] Early reperfusion of the ischemic area followed by coronary artery occlusion is extremely important and key component of management of ACS.[27]

However, the process of reperfusion may also cause myocardial reperfusion injury. Myocardial reperfusion injury is the death of cardio myocytes due to reperfusion after an ischemia. There is

no effective therapy to prevent this myocardial reperfusion injury in post revascularization patients.[28]

Photobiomodulation is found to be effective in preventing myocardial reperfusion injury in in-vivo and in-vitro animal models and a clinical human trial. Photobiomodulation in the form of low level laser therapy is a novel cardiac intervention which reduces the infarction size, decreases inflammation and scarring, improve cardiac damage markers and enhance tissue repair.[29] Low level laser therapy has shorter wavelength due to this it have not been very effective due to their inability to deeper penetration. Class IV laser therapy appears to be overcome this limitation due its longer wavelength and higher power output.[30]

1.1 Statement of Question

Is Class IV Laser therapy is effective in improving ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome?

1.2 Need of the study

Mainstay of treatment in acute coronary syndrome is reperfusion of the occluded coronary artery by pharmacological therapy and/or percutaneous coronary intervention and/or CABG which further causes reperfusion injury and still there is no any effective therapy to manage this reperfusion injury. Thus it's a neglected therapeutic domain in post revascularization patient. So there is a definite need to explore an effective conservative management tool to improve the clinical outcomes in individuals with acute coronary syndrome.

1.3 Aim of the study

To determine the efficacy of Class IV Laser therapy in improving ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome.

1.4 Objective of the study

1.4.1 To determine the effect of class IV laser on left ventricular ejection fraction (LVEF) in individuals with acute coronary syndrome who underwent coronary angioplasty

1.4.2 To determine the effect of class IV laser on Cardiac biomarker (Troponin I) in individuals with acute coronary syndrome who underwent coronary angioplasty

1.4.3 To determine the effect of class IV laser on functional outcomes in individuals with acute coronary syndrome who underwent coronary angioplasty

1.5 Hypothesis

1.5.1 Experimental Hypothesis: There will be a significant difference in ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome followed by class IV laser therapy.

1.5.2 Null Hypothesis: There will be no significant difference in ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome followed by class IV laser therapy.

1.6 Operational Definitions

1.6.1 Acute Coronary Syndrome: Acute coronary syndrome is an umbrella term which encompasses group of clinical symptoms which represent acute myocardial ischemia as a common end result and it includes unstable angina (UA), ST segment elevation myocardial infarction (STEMI), Non-ST segment elevation myocardial infarction (NSTEMI).[14-18]

1.6.2 Left Ventricular Ejection Fraction: LVEF is the fraction of chamber volume ejected during the systole in relation to the end diastolic volume.[31]

$$LVEF = (SV/EDV) \times 100$$

1.6.3 Cardiac Biomarker: Cardiac biomarker is a characteristic that can be quantified and measured as an indicator of biological process, pathogenic process or pharmacological response to a therapeutic intervention by cardiac myocytes which are used to accurate diagnosis, management and risk stratification of acute myocardial infarction.[32]

2. Review of Literature

This chapter deals with the review of literature associated with Acute Coronary Syndrome (ACS), its epidemiology, risk factor, pathophysiology and recommended medical, surgical or any other therapeutic interventions to manage acute coronary syndrome.

Acute coronary syndrome is an umbrella term which encircles a range of thrombotic coronary artery disease and refers to group of clinical symptoms which represent acute myocardial ischemia as a common end result; it includes unstable angina (UA), ST segment elevation myocardial infarction (STEMI), Non ST segment elevation myocardial infarction (NSTEMI). [14-18]

2.1 Epidemiology

A descriptive cross-sectional study was conducted in Khartoum State and Atabra (North of Sudan) to establish prevalence and risk factors for ACS among Sudanese individuals with diabetes mellitus. 496 (48.4% male and 51.6% female) individuals with DM were participated in the study out of which 27 (15 males and 12 females) had acute coronary syndrome. The prevalence of ACS was 5.44 %. The study revealed that albuminuria, HbA1C, HDL, triglyceride, LDL, gender and body mass index (BMI) was not associated with ACS while age, hypertension and chronicity of DM have a positive association with ACS. This study concludes that prevalence of ACS was 5.4% among Sudanese individuals with DM.[34]

A narrative review was conducted to review epidemiological data of coronary artery disease and acute coronary syndrome in low, middle and high income countries. In this review epidemiological study conducted from the year of 2000 to 2019 on coronary artery disease and acute coronary syndrome were included. Letters, editorials, conference abstract, reviews and

comments were excluded from the study. Burden of CVD were assessed among Low and Middle Income Regions and high income countries. Based on geography and income level, the World Bank has recognized six low and middle income regions globally and the rest of high income countries are not geographically distinct. The six low–middle income regions are East Asia and Pacific, Europe and Central Asia, Latin America and the Caribbean, the Middle East and North Africa, the South Asia region and Sub-Saharan Africa. East Asia and Pacific region is a most populated low-middle income region and almost 70% of the population of this region lives in china. The WHO and Global Burden of Disease reported the prevalence of angina was 8.2 million people and the number of DALY due to CAD was 11.8 million in EAP region, In China, CAD death rate is 64–106 per 100,000 among men aged 35–64 years. In last 20 years, CAD grown very rapidly and became the second leading cause of death. The incidence of CAD increased annually by 2.7% among males and 1.2% among females. In Chinese population ACS occurs 5 years earlier as compare to Caucasians and Latin American. According to WHO, in 2012 in Malaysia 20.1% of all the death were due to coronary artery disease. According to the National Cardiovascular Database of Malaysia, Malaysians population suffers from ACS at a younger age (mean age 55.9–59.1 years) compared to the most developed countries. According to Global Burden of Disease 30% of the mortality of ECA region is due to CAD. A study published in 2002, mortality due to CAD in all ECA countries was much higher than that of North America and Western Europe. According to the WHO GBD study 35% of the mortality of Lain America and Caribbean region was due to coronary artery disease. In Brazil, 820 deaths occur per day due to cardiovascular disease, Coronary artery disease accounts one thirds of these CVD deaths. In Middle East and North America regions, coronary artery disease was a leading cause of death, it accounts for 21% of mortality by 2001 which will be predicted to increment of

161% by 2020 as per the study of Global Burden of CVD. Populations of MEA are more prone to myocardial infarction at a younger age compared to other regions. Egypt is the most populated country of MEA region, Coronary artery disease accounts for 23.14% of mortality in 2014. Egyptians are suffering from ACS at younger age as compare to west. South Asian region is a most populated region in the world, where almost one fifth of global population is living. India is the largest country of this region. In 2001, coronary artery disease accounts for 13.6% of total mortality in this region. It reveals that more than one fourth of the CVD mortality among low-middle income countries occurs in SAR. South Asian are three to five folds more prone to myocardial infarction and also at younger age with more severity as compare to Caucasians. Coronary artery disease accounts for 15.5 % of total deaths globally and it rise as an epidemic in India. In 2015, coronary artery disease was a cause of death among 26.9% of medically certified deaths in India. Among the High income regions, in USA coronary artery disease is a leading cause of death in adults. It accounts for one third of all deaths in individuals older than the age of 35 years. It was reported that in 2013 in every 44 seconds one citizen of the USA will have a myocardial ischemia and almost every 1 min, someone will die due to coronary event. In UK, mortality due to cardiovascular disease was dropping but premature CAD mortality remains the same. Coronary artery disease is a leading cause of death in UK and Europe. This review revealed that incidence of coronary artery disease is decreased in developed countries but due to epidemiological transition prevalence of CAD is not reduced and may increase in the near future. Developing countries have variability among the incidence of CAD but due to globalization of western eating habits and sedentary lifestyle will lead to progressive rise in incidence of CAD.[4]

According to the global burden of disease study 2010, 24.8% of all the deaths in India were due to cardiovascular disease. The age standardized CVD death rate of 272 per 100000 populations

in India is higher than the global average of 235 per 100000 populations. Currently, there are no nationally representative surveillance data on the prevalence of CVD and the secular trends of CVD mortality in India. Ischemic heart disease and stroke is the most common (83%) among the CVD mortality, Ischemic heart disease is more prevalent than stroke. Both Ischemic heart disease and stroke are responsible for21.1% of all deaths and one-tenth of the years of life lost in India. The year of life loss due to CVD increases upto 59% from 1990 to 2010. The prevalence of IHD was 2% in 1960 in urban India which rise upto 14% in 2013 and was 1.7% in 1970 in rural India which rises to 7.4% in 2013. The Macroeconomic Commission for Health estimated that the absolute number of IHD patients in India will increase from 36 million to 62 million in ten years 2005-2015.[2]

2.2 Risk factors

A Cross-sectional study among 50 young adults reported in Emergency Department of a Rural Tertiary Care Hospital of Davanagere, Karnataka (India) with Myocardial Infarction. The mean age of participants were 38.1±5.8 years out of which 92% were males. Risk factors were smoking 36 (72%), diabetes 17 (34%), hypertension 6 (12%) and Body Mass Index (BMI) 36 (72%). Anterior Wall Myocardial Infarction (AWMI) was observed in 35 (70%) of subjects with angiography revealing Single Vessel Disease (SVD) 28 (56%), Double Vessel Disease (DVD) 5 (10%), Triple Vessel Disease (TVD) 3 (6%) and Myocardial Infarction with Non-Obstructive Coronary Artery Disease (MINOCA) 11 (22%). Three patients died during their course of treatment before initiating an interventional procedure. Smoking, diabetes mellitus and elevated BMI are major risk factor associated with ACS among young patients.[35]

A cross sectional study was conducted to access the prevalence of risk factors for coronary artery disease in rural population of north India. In this study 1078 residents of age ranges from 20

years to 60 years were randomly selected, out of which 980 individuals participate in the study. The individuals who were already diagnosed with any kind coronary heart disease were excluded from the study. 23.88% participants were between age group of 20 to 29 years, 25.51% between 30 to 39 years, 26.73% between 40 to 49 years and 23.88% were more than or equal to 50 years of age. The study found an overall prevalence of smoking was 10.9%, prevalence of smokeless tobacco was 37.5% and alcohol consumption was 21.4%. The prevalence of hypertension, Diabetes and obesity was 20.2%, 6.3% and 7 % respectively. 26.6% participants having systolic hypertension. This study reported a higher prevalence of behavioral risk factor of coronary artery disease.[36]

2.3 Pathophysiology

Acute coronary syndrome occurs as a result of vulnerable plaque rupture or endothelial ulceration, and a platelet associated disease process which leads to unstable angina, non ST segment elevation myocardial infarction, and ST segment elevated myocardial infarction.[14,19,37]

Initiation of Atherosclerosis: Atherosclerosis is an ongoing process of plaque formation which primarily occurs in the innermost layer i.e. intima of medium or large sized arteries. This atherosclerotic process progresses persistently throughout the life and ultimately leads to an acute ischemic event. A numerous coronary risk factors like hypertension, hyperlipidemia, smoking and diabetes adversely affect this process. These risk factors affect the endothelium of the arteries and causes endothelial dysfunction which initiates an atherosclerotic process.[14,38]

Progression of atherosclerotic plaque: when endothelium damaged, the inflammatory cells especially monocytes enter to subendothelium and undergo differentiation and transformed into macrophages. Macrophages engulf the oxidized LDL and penetrate the arterial wall and converted into foam cells. These foam cells forms fatty streaks, simultaneously these activated

macrophages release chemoattractents and cytokines which enhance the process by recruiting additional macrophages and smooth muscles cells. These Macrophages also activate matrix metalloproteinase enzyme which digest the extracellular matrix and leads to disruption of plaque.[23,38]

Stability of plaque and tendency to rupture: the stability of plaque varies according to inflammatory process. The ratio between macrophages and smooth muscle cells plays a vital role in vulnerability of plaque. Vulnerability of plaque also increases in case of high lipid core, thin fibrous cap, increased matrix metalloproteinase and intraplaque hemorrhage. Increased CRP has been found a positive correlation with plaque rupture.[14,39,40]

A plaque with a fibrous cap of less than 65 to 150 microns and a necrotic lipid core that involves more than 40% of the lesion can be defined as a "vulnerable plaque".[5]

Plaque disruption with systemic inflammation: Laboratory studies on human plaque indicate inflammatory mechanism as a key regulator of fragility of plaque. Macrophages establish a pathway for disruption of fibrous cap; macrophages activate matrix metalloproteinase and cathepsins. Thus increased level of proteinase and reduced tissue inhibitors leads to breakdown of extracellular matrix of plaque.[14,40,41]

Plaque disruption without systemic inflammation: Intense physical exertion and local mechanical stress on the arterial wall, either increased circumferential stress or reduced shear stress, may also lead to plaque disruption. The psychological stress activate sympathetic nervous system and release catecholamine associated with an increase in heart rate, blood pressure, and coronary vasoconstriction that may lead to plaque disruption and platelet activation, hypercoagulability,

and intense coronary microvascular constriction. Any type of physical or psychological stress is not enough to cause a coronary thrombosis but they can trigger instability in plaque.[42,43]

2.4 Clinical Presentation

Clinical presentation of ischemia include various combinations of chest pain, pain in upper extremity, jaw pain, epigastric discomfort, dyspnea, diaphoresis, nausea, fatigue, or syncope. There is a high rate of morbidity as well as mortality of coronary heart disease with an onset of chest pain, treating doctor consider a possibility of myocardial ischemia or unstable angina.[14,17,18] Chest pain or discomfort associated with ACS may occur with exertion or even at rest and it often diffuse instead of localized pain. ACS accounts for 20-25% of the chest pain reported in emergency department. There may be multiple causes of chest pain; differential diagnosis for chest pain[44] is given in table below:

Table 2.1 Differential Diagnosis of chest pain

Cardiac	Vascular	Pulmonary	Musculoskeletal	Gastrointestinal	Misc.
Acute Coronary Syndrome, pericarditis, hypertensive crisis, hypertrophic cardiomyopathy, tachyarrhythmia	Aortic dissection, large aortic aneurysm	Pneumothorax, Pulmonary embolism, pneumonia, pulmonary abscess, pleuritic	Rib fracture, sternal fracture, metastases, costochondritis, intercostal myalgia, neuralgia	Esophageal reflex, esophageal spasm, esophagitis, pancreatitis, biliary colic, diaphragmatic hernia, peptic ulcer, gastritis	Herpes zoster, anxiety, migraine, severe anemia

Literature supported to a progressive refinement in the characteristics of ischemic chest pain. The National Heart Attack Alert Program Coordinating Committee on recognition of symptoms associate with cardiac ischemia explained the presentation of ischemic cardiac pain: Pain, if present, is described as pressure, tightness, or heaviness. It may radiate to the neck, jaw, shoulders, back, or one or both arms, pain similar to prior ischemia, and change in pain pattern over the prior 24 hours. The pain may also be described as indigestion or heartburn with associated nausea and/or vomiting. Additional symptoms in the absence of pain may include shortness of breath, weakness, dizziness, lightheadedness, or loss of consciousness. In a review, it was stated that among physical finding hypotension (SBP < 100mmHg) was strongest predictor of ACS.[44,45]

A case control study among young adults with acute coronary syndrome was conducted in Spain to determine the clinical and prognostic characteristics in ACS. 123 young adults of age less than 40 years who were diagnosed with ACS were recruited in the study, 59.3% were diagnosed with STEMI, 23.6% with NSTEMI and 17.1 % were having unstable angina. 44.7% of participants having Single vessel disease, 20.3% having double vessel disease and 5.7% were having triple vessel disease. 39.2% patients were having myocardial infarction of inferior wall, 30.4% having MI of anterior wall and only 3.9% having MI of lateral wall while among 26.5% of patients having not locatable MI. PCI was performed in 52.1% and 8.1% underwent bypass grafting. In 52 weeks of mean follow up duration, 26.4% patients were readmitted out of which 48.3 % having acute myocardial infarction. Decreased LVEF and smoking were associated with readmission.[46]

After initial clinical presentation a numerous factor that define the prognosis of it. After acute coronary syndrome myocardial dysfunction is very common and it may cause heart failure.

Myocardial dysfunction leads to dynamic changes in left ventricular ejection fraction; on the other hand some patients may be asymptomatic despite of altered systolic function of left ventricle. Left ventricular systolic dysfunction is the single and strongest predictor of mortality in individuals with acute coronary syndrome.[47]

A cohort study was done to identify factors associated with mortality on the basis to left ventricular ejection fraction at the time of 1st admission in ACS individuals. In this study 8983 patients with ACS were recruited and they were categorized on the basis of LVEF at the time of admission. 845 participants have severe LV dysfunction, LVEF < 30%; 4470 participants have moderate LV dysfunction, LVEF = 30-49% while 3659 participants have preserved LVEF ≥ 50%. The result of this cohort reveals that mortality rate was highest (36%) in participants, who have severe LV dysfunction.[48]

2.5 Quality of life

Early diagnosis, prevention or limits the myocardial injury and short term mortality are important outcome in individuals with acute coronary syndrome, but understand or assess their quality of life after survival is also an important aspect.

A descriptive study was conducted in Kerala (India) to evaluate health related quality of life among 1261 ACS survival after 30 days. In this study, translated version of Seattle Angina Questionnaire was used to assess quality of life. Among old age respondent higher angina frequency, greater physical limitation and low treatment satisfaction rate were observed. Physical limitations among females were greater as compare to males. This study concludes that overall treatment satisfaction rate was high but overall quality of life was poor.[49]

A study was conducted in Maharashtra (India) to assess quality of life after myocardial infarction among women. 50 women with MI who underwent PTCA and reported for follow up were included in this study. Quality of life was assessed using Mac New Heart questionnaire. The results of this study reveal poor score in all three domains (emotional, physical and social) among women post MI.[50]

2.6 Diagnostic measures

Acute coronary syndrome may be suspected in all the cases of ischemic pain. Apart from the clinical presentation of the patient, past medical history is essential to make an appropriate diagnosis. Prior history of coronary artery disease, hypertension, nature and onset of the angina, any associated risk factor should be evaluated in past medical history.[16,18]

Symptoms of unstable angina, NSTEMI and STEMI having same clinical presentation so to differentiate it, a medical evaluation and 12 lead ECG is must. As per the 2007 guidelines for manage Unstable Angina/ NSTEMI by American College of Cardiology and American Heart Association, any individuals with suspected symptoms of ACS should be immediate refer to a medical facility where 12 lead ECG, cardiac biomarker assessment and evaluation by a Physician is possible.[51,52]

Electrocardiogram: The American Heart Association/ American College of Cardiology suggest that when an individual with symptoms of ACS reported in triage, a 12 lead ECG should be performed within 10 minutes. ECG helps to establish a diagnosis as well as risk stratification.[14,52,53] ST segment depression, transient ST segment elevation and/or T-wave inversion are common findings of ECG which are associated with unstable angina and present in 30% - 50% of patients. A minimal deviation of ST segment is an important indication of

ischemia and a specific measure of prognosis. T wave inversion is a sensitive indication for ischemia but it is more specific when more than 0.3mV. An ST segment elevation of 0.1 mV or more in at least 2 continuous lead indicate acute myocardial infarction; which should be confirmed by cardiac biomarker.[21,54]

Cardiac Biomarker: when there is ischemia for a prolonged period of time it will lead to necrosis. If ischemia can rule out earlier, necrosis can be prevented. The cardiac biomarkers are useful to detect ischemia at any phase of this process.[14] So the American college of Cardiology and European Cardiac Society incorporated these biomarkers in the guidelines to diagnosis and management of acute coronary syndrome and acute myocardial infarction.[55] Diagrammatic presentation of coronary vessel occlusion to ischemia to infarction is given below:

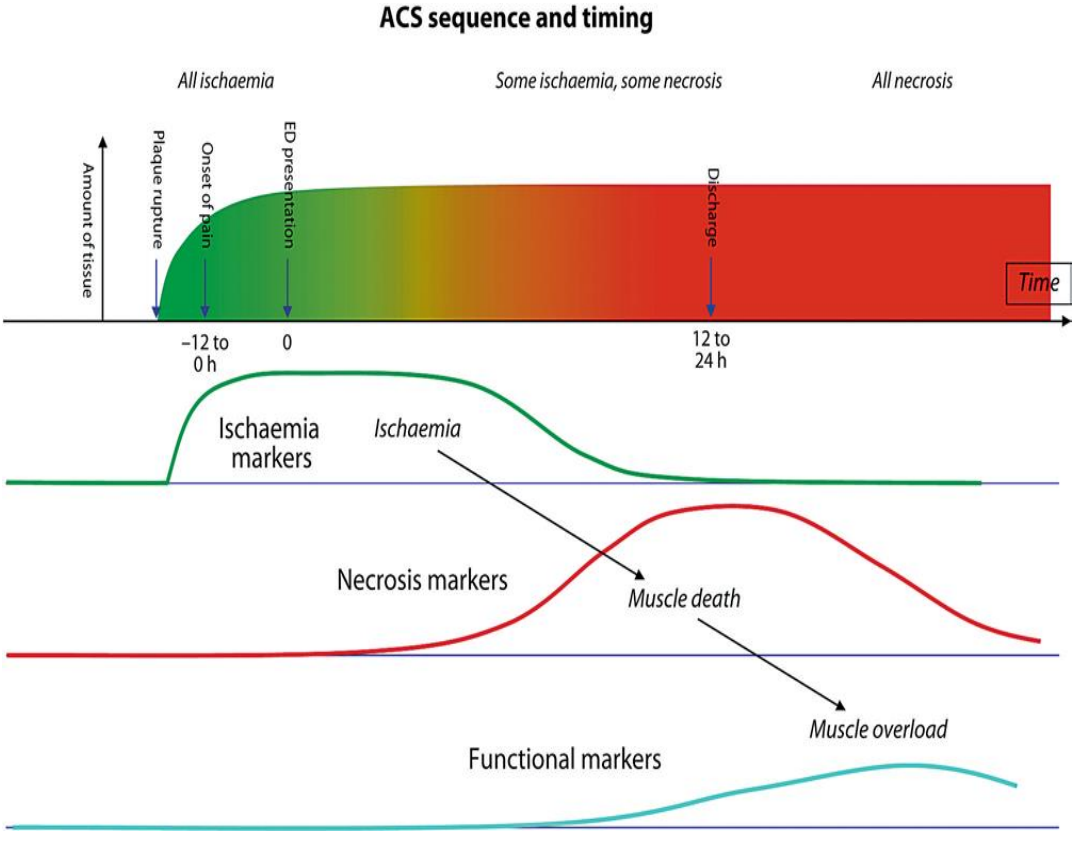


Figure 2.1: Progression of vascular occlusion to ischemia and infarction[55]

Biomarkers of Ischemia:

Choline: Choline is released by phospholipase D to yield plasma choline. Choline is released in numerous processes plaque disruption is one of them.[56] Macrophages in an atherosclerotic event produces phospholipase, injury of ischemic membrane also breakdown the phospholipids, both of these processes release choline in to the plasma. From plasma these choline are taken up by erythrocytes via choline receptors. Choline is released during the early stage of ischemia, so it's helpful to detect ischemic changes in early phase and limits the ischemic injury. Increased count of whole blood choline in HPLC - mass spectroscopy is an indication of acute coronary syndrome.[57,58]

Unbound Free Fatty Acid (FFAu): Free fatty acid (FFA) release from the muscles tissues, especially cardiac muscles when there is ischemia. Large amount of free fatty acids bounds with albumin, but little amount of free fatty acids is found in the serum which is known as unbound free fatty acid (FFAu). In an experimental study it is found that there was a significant increase in FFAu followed by 30 minutes of ischemia induced by balloon angioplasty as compare to pre-procedure FFAu, while ST segment changes were observed in only 50% of participants and associated with highest values of FFAu.[55,59]

Ischemia modified Albumin (IMA®): Myocardial ischemia leads to acidosis and release of free radicals, free copper & zinc. The N-terminus of albumin not binds with transition metals like cobalt II, nickel II and copper II ions. Myocardial ischemia results to decrease in ability of albumin to bind with cobalt. Albumin cobalt binding test (ACB® test) for IMA is based on this albumin cobalt binding relationship. Amount of unbound cobalt is assessed by adding a measure

amount of cobalt into the test sample and identify colourimetrically followed by addition of dithiothreitol. The amount of unbound cobalt is directly represents the IMA.[55]

Biomarkers of Necrosis:

Myoglobin, CK-MB, Troponin I (cTnI), Troponin T (cTnT) is the cytosolic markers which are considered as arbiters for diagnosis of acute myocardial infarction.[60] Cardiac troponin found in the cardiac muscles and it released when there is any injury myocardial injury. Literature suggest that there is no elevation in the cardiac troponin when there skeletal muscle trauma. So, Cardiac troponin is considered as the gold standard test to diagnose myocardial necrosis.[55] Cardiac troponin can be easily detected in serum within 3-4 hours of myocardial damage and troponin I remain elevated upto 5 days and troponin for 10 days. Both short term and long term follow up shows that an elevated troponin is associated with an increase rate of major adverse cardiac event.

Cardiac troponins are the most specific and sensitive biomarker to myocardial damage but acute coronary syndrome is not an only cause of its elevation.[61] It can be increase due to other conditions like renal failure, percutaneous coronary intervention or any drug related cardiotoxicity that may lead to myocardial damage.[62]

Biomarkers of cardiac dysfunction:

There are some specific cardiac biomarkers which indicate the dysfunction of the myocardium. Atrial natriuretic peptide are the biomarkers which produced by the atrium of heart in response to sudden change in the volume of atria.[55]

B-type Natriuretic Peptide (BNP) are the biomarkers which produced by the myocytes of the ventricular wall in response to excess ventricular stretch.

C-type Natriuretic Peptide is produced by endothelium of heart.

D-type Natriuretic Peptide is the found in green mamba.

Other investigations:

A chest radiograph should be obtained to rule out other possible cause of chest pain.

As per the guidelines of National Cholesterol Education Program Adult Treatment Panel III and American College of Cardiology/American Heart Association a complete lipid profile should be assess within 24 hours of onset of ACS.[14]

After acuter coronary syndrome, LVEF assessment is indicated to define the prognosis and selection of treatment strategy[26] and it is a Class I recommendation as well as core performance measure recommended by American College of Cardiology (ACC) and American Heart Association (AHA).[25]

Guidelines by ACC/AHA for ST-Elevated Myocardial Infarction (ACC/AHA STEMI) suggests that contrast left ventriculography to be done at the time of cardiac catheterization and transthoracic echocardiography (TTE) should be performed on the second/third post admission day for cases in which mechanical complications are suspected. In patients with moderate to severe LV dysfunction, a reassessment of LV function at least 40 days later is strongly recommended to guide the need for device-based therapy. [26]

Functional status and Quality of life can be assessed by self-administrated questionnaire; a number of questionnaires are available to assess health related quality of life among individuals with cardiac disease like EQ-5D, WHOQOL, HeartQOL, MacNew Heart related Quality of life (MacNew) questionnaire, Seattle Angina Questionnaire (SAQ), SF-36.

Seattle Angina Questionnaire: is a self-administrated questionnaire to measure functional status among patients with coronary artery disease. It measure a spectrum of health related quality of life by assessing 5 major domains including physical limitation, angina stability, angina frequency, treatment satisfaction and quality of life.[63,64]

2.7 Management

It is essential to examine patients with suspected ACS immediately to prevent possible fatal clinical consequences and resolve ongoing myocardial ischemia. Early risk stratification should be performed which includes demographic and medical history of the patient, physical examination, ECG, cardiac biomarker evaluations and risk assessment tools may also be used to predict risk of recurrent ischemia or death following an ACS event.[14] Early risk stratification helps in determining whether a patient should be managed either conservatively or an early invasive intervention is needed as well as it also helps to determine the pharmacologic therapies. The timely reperfusion of the occluded coronary artery is of the utmost importance in the management of ACS.[27,16]

Antipletelet therapy: adequate patency of coronary vessels doesn't guarantee on perfusion of myocardial tissue. Thrombolytic treatment has three important limitations in this respect. First, the occluding thrombus may breakdown in smaller parts as a result of treatment which causes distal micro embolization. Second, treatment with a thrombolytic agent only resolves the fibrin-rich red part of the thrombus, the platelet rich white part remains largely untouched. Third, fibrinolysis generates raised concentrations of free thrombin, and activates platelet aggregation, which might cause a further worsening of the microcirculation. To overcome these limitations, combine fibrinolytic treatment with aggressive anti-platelet therapy were recommended. Well-

established antiplatelet therapies in the management of ACS include aspirin, adenosine diphosphate P2Y receptor antagonists, and glycoprotein IIb/IIIa inhibitors. Aspirin should be started as soon as possible after an ACS event with an initial loading dose of 162–325 mg. Aspirin is a weak antiplatelet as it inhibits only one pathway leading to platelet aggregation. The combined glycoprotein IIb/IIIa inhibitors and fibrinolytic therapy achieve complete reperfusion than fibrinolytic alone.[14,16]

Anticoagulant therapy: In addition to antiplatelet therapy, low molecular weight heparins are recommended in the acute phase of non ST segment elevation prior to angiography. Commonly used agents include enoxaparin, dalteparin and tinzaparin. Anticoagulation is not routinely prescribed long term following ACS.[17]

Coronary Revascularization: In case of coronary obstruction, revascularization should be performed as early as possible, it can be performed by PCI or CABG. SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) helps treating doctor to make a decision, as it represents a latest and comprehensive comparison between PCI and CABG so it should be considered during revascularization recommendations.[65]

Percutaneous coronary intervention (PCI): Reperfusion therapy should be administrated to all the eligible individuals with STEMI within the 12 hours of onset of symptoms. Percutaneous Coronary Intervention is the recommended method of reperfusion. Results of randomized trials have shown better clinical outcomes among individuals who underwent mechanical reperfusion than the individuals who managed by pharmacological intervention. In 1999, American Heart Association/ American College of Cardiology recommended PCI as an alternative to fibrinolytic therapy. As per the guidelines of European Society of Cardiology, Percutaneous Coronary

Intervention was preferred therapeutic option with the goal of time from door (first medical contact) to balloon (device time) less than or equal to 90 minutes.[14,16,66]

Coronary Artery Bypass Grafting: the use of CABG in individuals with acute coronary syndrome is decreased in the past decades due to increase use of percutaneous coronary intervention. However long-term advantages are seen in the individuals who underwent CABG as compare to PCI, on the other hand a study conducted among the individuals with left main coronary artery disease who underwent either PCI or CABG, reveals that there is no significant difference in the outcomes after 5 years between PCI and CABG.[67]

2.8 Alternative or complementary therapy in Acute Coronary Syndrome

An experimental study was conducted to evaluate the effectiveness of Reiki treatment on HRV in patients recovering from acute coronary syndrome. 229 patients were screened within 72 hours of admission to receive Reiki, out of them 49 met the inclusion criteria and signed the informed consent. Throughout the baseline and intervention, patients lie supine. The patient in Reiki group, Reiki trained clinical nurse placed his/her hands on patient's head and torso in 7 positions. Second music group purposed to induce relaxation without touch, meditative music with tempos slower than normal resting heart rate. Continuous ECG and HRV were analyzed with holter monitoring. Emotional status was assessed by 10 point Likert scale. High frequency power (0.15-.40 Hz), a marker of parasympathetic activity was compared. HF HRV increased significantly in Reiki group, whereas overall decrease in music change and no change in control group. Emotional status also improved in the Reiki group followed by music and control group. This study suggests that Reiki significantly increased vagal activity and is a safe and feasible intervention in acute care settings.[68]

A double blinded placebo controlled clinical trial was conducted to examine the effect of localized heat therapy over chest on physiological parameter in individuals with acute coronary syndrome. 66 patients diagnosed with ACS were randomly divided in two, experimental and placebo controlled group. Experimental and placebo controlled group received four sessions of localized heat therapy with hot pack warmed at 50^0C and 37^0C respectively for 23 minutes over anterior chest. Heart rate, Respiratory rate, arterial blood pressure, blood oxygen saturation were measured at baseline and after intervention. There was no significant different among heart rate and arterial blood pressure between the groups, but within the experiment group there was a significant decrease in blood pressure. While respiratory rate was decreased and blood oxygen saturation improved significantly as compared to placebo controlled group. This clinical trial suggests that localized heating therapy has beneficial effect on physiological parameters among individuals with acute coronary syndrome.[69]

An experimental study was conducted to examine the effect of moderate intensity aerobic physical training on inflammatory parameters in individuals with stable coronary artery disease. In this study 52 individuals with stable coronary artery disease were divided into two groups. There were 22 individuals in group I, who received moderate intensity aerobic physical exercise as cardiovascular rehabilitation program for 3 weeks and continuing 3 weeks at their home. In group II, 30 individuals who didn't have physical training in last six months after their cardiovascular rehabilitation program. BMI, High sensitive C reactive protein (hsCRP), ICAM-1 and VCAM-1 was assessed at baseline and after six months. Results of this study reveal that BMI was significantly improved in the physical training group. There was a significant reduction in the hsCRP and VCAM-1in the physical training group as compare to control group. This conclude that moderate intensity physical training is beneficial for primary as well as secondary

prevention of coronary artery disease as physical exercise reduced the inflammatory state and obesity without affecting visceral obesity.[70]

Now a days Laser therapy is also being used to improve wound healing and manage post-operative pain in individuals who underwent cardiac surgery through median sternotomy. Previously Low Level Laser Therapy (LLLT) was used in clinical settings as a therapeutic modality which gives better outcomes on wound healing and pain management, apart from this low level laser therapy shows significant results in cases of myocardial injury followed by myocardial ischemia as well as in myocardial reperfusion injury. Effects of LLLT in cases of myocardial injury are well documented in in-vivo and in-vitro animal models as well as in human clinical trials.

2.9 Laser

In the ancient time around 6th century B.C. heliotherapy or light therapies have been used around the world.[71] Laser is the most advanced source of light and is an acronym for Light Amplification by Stimulated Emission of radiation. Low level laser therapy has been applied clinically for lase decades.[72]

Classification of laser: the international system of laser classification is concerned only with the potential for causing injury to eye or skin. They are defined in the ANSI Z136.1-2007 (IEC 60825) international standard or the USA standard.[73,74]

1. Class 1 laser are considered incapable of producing any potential damage, non-destructive and exempted from any kind of monitoring.

2. Class 1M lasers are harmless during the normal operation but they can be hazardous if viewed through an eye cup or a telescope.

3. Class 2 laser producing visible spectrum radiation (400-700 nm), and eye protection is afforded by the aversion response, which lasts around 0.25 seconds. In the previous classification system it was class 2 and class 2a lasers, but now it is Class 2 and Class 2M. Class 2 lasers are also exempted from any kind of monitoring, but class 2M may require depending on the application.

4. Class 3: Class 3 has two subcategories: 3R and 3B. The 3R laser does not require any training or medical supervision. Class 3B can be hazardous when reflected directly and specularly.

5. Class 4 Laser: Class 4 lasers can cause serious hazards. In actuality, direct beams from class 4 lasers are hazardous to the eye and skin, causing diffuse reflection or fire. Other probable adverse effects of Class 4 lasers include laser-generated air pollution and hazardous plasma radiation.

LLLT has been found beneficial in pain management, inflammation reduction and fasten tissue healing, but it has shorter wavelength and low power output so it has less penetration due to this it is unable to get desired effects on deeper tissues. LLLT with Class IV laser therapy has longer wavelength and high power output which overcome the penetration issues of Low level laser therapy. Recently, Class IV laser therapy is also being used in numerous sports and musculoskeletal conditions as well as it gives beneficial effects and its feasibility is also assessed as a part of a multi-model analgesia in post-cardiac surgeries.

2.9 Laser Therapy in Cardiac Conditions

A double blinded clinical trial was conducted to examine the efficacy of low level laser therapy for reducing acute pain followed by sternotomy among individuals who underwent CABG. 90 individuals who underwent elective CABG were randomly divided in to control, placebo and laser group of equal size. Pain during coughing was primary outcome measure and assessed by the VAS and McGill Pain Questionnaire from day 2 to 1st month of surgery. There was a significant decrease in the pain all groups from post-operative day 2 to post-operative day 8 and complete absence of pain after one month. While Laser group having less pain score on 6th and 8th post-operative day in both VAS and McGill Pain Questionnaire scale as compared to control and placebo group. This study concludes that LLLT seems to be effective in post-operative pain reduction among individuals who underwent CABG.[75]

An experimental study was conducted among 47 female Wistar rats to evaluate the beneficial effect of Low Level Laser Therapy in early post-infarction cardiac remodeling could remain in progressive heart failure with the interference of irradiations. Myocardial infacrtion was produced in all the rats by permanent coronary occlusion. All the rats were randomized in to infarcted rat non-treated with LLLT (MI-N), Sham Rats and infarcted rat treated with LLLT (MI-LLLT). Sham rats were operated on the same day. Sham and MI-N group were subjected to LLLT but the device turned off. Echocardiography was performed o 3rd day and after 5 weeks. Rats with an infarct size $\geq$ 37% of left ventricle were included in the study. LLLT was given after 60 seconds and 3 days post coronary occlusion. On the 3rd day, there was no difference in the collagen content among all the groups while on the 5th week, infarcted rats present with a significant increase fibrosis and LLLT has no effect on this. LV diastolic diameter was higher in MI-LLLT group while systolic diameter was high in infarcted groups as compare to sham group,

but on the 5th week, both systolic and diastolic diameter were significantly high in all infarcted group as compare to sham group. Beneficial effect of LLLT was noticed on cardiac remodeling in early post MI phase (3 days). Fraction shorting was significantly high in the MI-LLLT group as compare to MI-N. This study concludes that LLLT improves LV systolic function in early post MI cardiac remodeling and these effects depend on the maintenance of phototherapy.[76]

A study was conducted to examine the effect of LLLT versus trunk stabilization exercise on sternotomy healing post coronary artery bypass grafting. 45 individuals with a mean age of 52.8 ± 3.29 years with acute sternal instability after CABG were recruited and randomly divided in to three group. Laser group received LLLT with routine cardiac rehabilitation, exercise group received trunk stability exercise along with routine cardiac rehabilitation and control group received routine cardiac rehabilitation only. Sternal separation measures at upper, middle and lower level. The pre-treatment score at upper level was 0.172 ± 0.07, 0.17 ± 0.04 & 0.194 ± 0.06 and post-intervention of 4 weeks it was 0.13 ± 0.03, 0.154 ± 0.04 and 0.171 ± 0.05 in laser group, exercise and control group respectively. At middle level before inter invention it was 0.199 ± 0.1, 0.232 ± 0.05 & 0.218± 0.08 which decreased up to 0.155 ± 0.06, 0.187 ± 0.04 and 0.02 ± 0.05 post-intervention for 4 weeks in laser group, exercise and control group respectively. At lower level base line score was 0.238 ± 0.12, 0.3 ± 0.1 & 0.263 ± 0.12 which decreased upto 0.2 ± 0.11, 0.242 ± 0.08 and 0.258 ± 0.08 after intervention of 4 weeks in laser, exercise and control group respectively. Median sternotomy photographic analysis was done by photography, pain was assessed with VAS and pre-treatment score was 87.06 ± 5.76, 84.92 ± 7.17 and 83.9 ± 6.73 in laser, exercise and control group respectively which decreased up to 12.17 ± 4.34, 16.63 ± 3.82 and 32.88 ± 8.61, respectively after 4 weeks intervention. Functional status was assessed with ADL performance scale through interviews with the patients. The baseline score of ADLs

was 2.86 ± 0.99, 2.8 ± 1.32 and 2.6 ± 1.29 in laser, exercise and control group respectively which improved upto 9.4 ± 0.63, 9.26 ± 0.45 and 6.26 ± 1.16 post-intervention. This study revealed that after completion of 4 weeks, LLLT was found more efficacious than trunk stabilization in decreasing pain, sternal separation and improving activity of daily living.[77]

A system review was conducted in which 23 studies were reviewed from in vitro cardiomyocyte culture to human trial. Out of these 23 studies, 17 were conducted on animal models, 2 were conducted on isolated heart of rats, 3 on cell cultures and 1 was a human clinical trial. In the animal models, photobiomodulation or laser therapy site was different according to their experimental design; in 12 studies myocardium was irradiated directly, in 6 studies they use transthoracic laser therapy (with shaved or removed skin) and in 3 studies they irradiated distal to the heart over leg muscles or tibia. In human clinical trial transthoracic laser application was used. Laser therapy or photobiomodulation was given as preconditioning treatment, post conditioning treatment, during surgery, post reperfusion, or in combination with other treatment. Total dose used for photobiomodulation ranged from 0.6 J to 36 J with a mean of 6.26 J by using laser of a wavelength from 630nm and 830nm. In human clinical trial they used laser of 810nm wavelength and total energy of 6 J. The most significant result from this review was modulation of infarct size and improvement of cardiac remodeling due to the application of photobiomodulation. Three studies reported more than 60% reduction in total infarction size. One study reported that the reduction in the infarction size significantly higher (76%) when laser radiation was applied directly over the tibia compared to 31% reduction when applied locally to myocardium. One study reported that higher dose of photobiomodulation was more effective in initial phase of myocardial ischemic reperfusion to reduce injury, it suggest that 804nm LLLT at 12mW/cm^2 has more effective cardio-protective mechanism that 6mW/cm^2. The study further

suggest that most effective dose given 1.5 hour after the myocardial ischemic reperfusion being a combination of 12mW/cm^2 and 5mW/cm^2 which was superior to two dose of 12mW/cm^2. Moreover, the power density required to achieve a desired effect on myocardial infarction size reduction was similar for rats, dog and humans. If delayed post conditioning treatment was omitted from the treatment regime, the effect on myocardial size was reduced. Literature supposed that transthoracic photobiomodulation may not reach a therapeutic dose upto the cardiac tissue in humans. Transmission of light to the cardiac tissue in humans does not appear in the literature, it's inferred from the other similar study in which photobiomodulation is used to treat traumatic brain injury they suggest that transcranial LLLT can reach therapeutic doses upto 40-50 mm deep with infrared radiation. The average parasternal skin to heart depth in humans has been reported as 32.1±7.9 mm. There is a clinical trial which reported the transthoracic application of LLLT leads to changes in cardiac biomarkers. This review concluded that photobiomodulation may have a cardioprotective agent to prevent myocardial ischemic reperfusion injury and could protect against the initial ischemic event and prevent from the ongoing damage due to reperfusion. Photobiomodulation can improve tissue responses, reduced infarction size and lower the rate of restenosis. It is an effective post-conditioning therapeutic protocol which prevents MIR injury and extends the available time for intervention to treat MIR injury.[29]

An experimental study was conducted to determine the effect of class IV laser to increase vasodilation and limb blood flow to the soft tissues of the forearm. The primary outcome measure for the experiment was percentage change in the circulation of the forearm (mL/min per 100 mL tissue). In this study 10 healthy male individuals with a mean age of 20.80±2.16 years and voluntarily signed the informed consent were recruited. Participants were randomly divided

into 4 groups; A, B, C (Sham) and D. A crossover, repeated-measures design was used to measure blood flow changes in the forearm before (baseline), during and after a 4-minute laser treatment session. Laser treatments were administered during all 4 sessions accompanied by venous occlusion plethysmography (VOP) measurements. Group A was irradiated with 1W, group B was irradiated with 3W, group C was Sham group and group D with 6W. All the groups were treated for 4 minutes with 50% of duty cycle. Only group B which was irradiated with 3W, shows an increase in FBF from baseline over time. The sham, 1-W, and 6-W groups did not display any increases in FBF at any time point. This suggests that a properly designed laser treatment protocol with appropriate dosing guidelines is a viable therapy to increase limb blood flow. Laser therapy's ability to increase blood flow in a dose-response manner is therefore an effective, noninvasive treatment modality to improve blood flow and may promote tissue healing in the clinical setting.[78]

An experimental study was conducted to examine the effect of low level laser therapy on cardiac biomarkers among post CABG individuals. In this study 60 individuals with double or triple vessel disease who were planned manage by bypass grafting were recruited and randomly divided into Control and experimental group. CBC and Cardiac Biomarkers (CPK, CPK-MB and LDH) were assessed before the surgery. 32 individuals in experimental group were irradiated with 810nm, 500mW gallium aluminum arsenide (GaAIAs) diode laser was used for 3 successive days post-surgery. The irradiation was performed by contact method over the incision and over the pericardium (left parasternal 2^{nd}, 3^{rd} intercostal spaces and apex). CBC and Cardiac Biomarkers were reassessed at one hour and 12 hour after daily laser irradiation and at the time of discharge on 5^{th} day. On the other hand, control group was reassessed at the same time. The results of this study indicate that there was a significant difference in WBC (8.43 ± 4.28 and 9.94

± 3.27 pre and post intervention respectively), Neutrophil (83.73 ± 87.62 and 70.62 ± 9.41 pre and post intervention respectively) and lymphocyte (11.5 ± 7.91 and 22.93 ± 8.09 pre and on 5th day post intervention respectively). There was a significant statistical difference was seen in CPK, CPK-MB, LDH cardiac enzymes over time but there was no significant difference between the groups. The study concludes that LLLT post CABG may decrease cardiac cellular damage and enhance the tissue repair.[79]

An open observation prospective pilot study was conducted to assess the feasibility and efficacy of class IV laser on post-operative pain relief among individuals who underwent CABG. In this study 100 adults with a mean age of 59.63 ± 9.38 who underwent off-pump CABG were recruited on the basis of inclusion & exclusion criteria and all the participants were received post-operative analgesia as per the standard institutional protocol. The pain was assessed by 11 point Verbal Rating Scale (VRS). Class IV laser therapy was given on POD 1, after 30 minute of extubation as once a day for next 2 days at the same time if VRS score was more than or equal to 5. The LCT-1000^{TM} (Litecure Medical) laser was used with dose of 10J/cm2 over an area of 150cm2 (approx.) of sternum covering the incisional wound for 150 seconds. The VRS score was assessed immediately before laser, 1hour after the irradiation and thereafter every 6th hourly till 72 hours following first laser application. The incisional wound was examined everyday for any complication. The means VRS of all the participants before laser application was 7.31 ± 0.94, which reduced upto 4.0 ± 1.279 after 1 hour of laser application and upto 3.40 ± 2.697 after 24 hours of first laser application. Only 40 patients had VRS ≥ 5 at 24 hours of first laser application, they were irradiated the second dose and in the next 6 hours (after 30 hours of first application) the VRS reduced from 6.38 ± 0.87 to 3.15 ± 1.51. and the pain score became 0 at 54th hours. None of the patients required third dose of laser therapy. This study concludes that

class IV laser can be an effective modality to manage post-operative pain following CABG. It can be considered as a component of multimodel analgesia (MMA) technique.[30]

An experimental study was conducted to determine the cardioprotective effect of induction of autologous bone marrow cells by LLLT and its effects on heart function in infarcted porcine heart post myocardial ischemia and reperfusion. Myocardial infarction was induced by interrupt the blood supply to myocardium by balloon inflation in the middle of left anterior descending coronary artery for 90 minutes among farm pigs. Post ischemic myocardial scarring was assessed by histology and MRI and heart function was assessed by echocardiography, immediately post reperfusion. Cardiac biomarkers (troponin I, CPK) and antioxidant in the blood were measured before MI, 3 hours post MI, 5 hours post MI then every day for 7 days. Recruited pigs were randomly divided in to experimental and sham control group. Laser radiation was given over MNCs enriched area on ileum and tibia. Most of the area in ileum is enriched with MNCs while in tibia MNCs concentration is higher close to the proximal end. So laser was given over flat area of ileum and over proximal end of both the tibia. 808 nm Ga-Al-As diode laser with a power output of $10mW/cm^2$ for 100 seconds was after 30 min, 2 days, and 7 days post-induction of MI. Control group was treated similarly but the laser kept off. 24 hours post intervention stem cells in the blood of experimental group was 2.62 times higher than the control group post 48 hours. The infarction size ($5.2 \pm 0.82\%$) was significant lower in the laser treated experimental group as compare to sham control group $16.6 \pm 3.7\%$. The left ventricular ejection fraction was significantly higher in laser treated group than the non-laser treated group. At 24 hours post MI, the troponin I level was significantly lower in the laser treated group than the non-laser treated group while at 48 hours troponin I level was equal in both the groups. CPK accumulation upto 24 hours in blood was significantly lower in the laser treated group. On the

other hand the antioxidant levels in the blood were significantly higher in laser treated experimental group than the sham controlled group. The study concludes that LLLT to bone marrow has beneficial effects in ischemic heart at acute as well as long term phase. The cardiac markers (troponin I & CPK) were also lower which leads to reduction in scarring, thus it have a cardioprotective mechanism and improve the functional status of heart in post MI condition.[80]

A randomized double blinded study was conducted to analyze the healing effect of low level laser therapy on median sternotomy incision among individuals who underwent elective on pump coronary artery bypass grafting. In this study 90 participants were randomly divided in to control, laser and sham groups, each group having equal number (n=30) of participants. Laser group was irradiated with low level laser (λ = 660nm, energy density 6 J/cm^2) immediately after surgery and on 2nd, 4th, 6th and 8th postoperative day. Sham group was subjected to laser irradiation but the equipment kept off and the control group underwent assessment and follow-up only. The incision healing was assessed in context of color, wound closure and texture with the help of photographs. Photographs were taken immediately after the surgery and post interventional assessment was done on 8th post-operative day. The Laser group shows less hyperemia, less incisional bleeding and no dehiscence. One participant from the sham group and two participants from control group developed dehiscence during first month post- surgery.[81]

Table 2.2: Studies using laser therapy in cardiac condition

Author	Year	Sample	Outcome measures	Intervention	Conclusion
Animal model					
Ad N. et al[82]	2000	41 rats (22 in experimental group & 19 in control group)	Infarct size	Trans thoracic Low level laser therapy; 804nm, 4.5 J (60seconds post MI for 10 minutes for 3 days)	Effective to reduce infarction size post myocardial ischemia Infarction size is 2.7 times higher in control group
Gatsura S.V. et al[83]	2002	42 rats (10 in control group and 16 in LELI for 2 minutes and 16 in LELI for 15 minutes)	Infarction size, Hemoglobin affinity for oxygen	Trans thoracic laser irradiation; 660nm, 0.018 J and 0.138 J (4 hours post reperfusion for 2 minutes and 15 minutes respectively)	15 minutes LELI reduces infarction size post 4 hours of reperfusion MI area (% of weight of LV) in control group was 47.38±0.45, 45.69±0.76 in 2 min LELI group and 37.81±1.09 in 15 min LELI group
Hentschke Vitor S. et al[84]	2012	49 rats (8 P-sham, 8 in 3J/cm^2- sham, 8 in 21J/cm^2- sham, 9 in P-HF, 8 in	Inflammatory profile, infarction size	Low level laser over right gastrocnemius; 660 nm, 14.7 J 73.5 seconds, 2.1 J 10 seconds	LLLT have systemic & skeletal muscle anti-inflammatory effects in rats with HF, cab be used in

		3J/cm^2- HF, 8 in 21J/cm^2- HF		after 4 weeks of MI	Pro-inflammatory state in HF
Keszler Agnes et al[85]	2014	Mice	Myocardial protection in hyperglycemic condition	NIR radiation over epicardial surface by LED; 670 nm, 51J for 60 seconds before and first 4 minutes during reperfusion	Protects myocardium against infarction via NO dependent / NOS independent mechanism and reduces ROS.
Keszler Agnes et al[86]		Mice	Cardioprotection under diabetic and normal condition	NIR radiation over epicardial surface by LED; 660 nm, 8.5J for 60 seconds before and first 4 minutes during reperfusion	Protects myocardium against infarction via NO dependent / NOS independent mechanism and reduces ROS. MI size (% of LV area of risk) was 51±4 in control group while 31±7 in experimental group.
Lohr Nicole L. et al[87]	2009	28 rabbits randomized in 4 groups	Cardioprotective effect via NO release from HbNO and MbNO	NIR radiation over myocardium just prior to ischemia and	Photodissociation of HbNO and MbNO by NIR increases the release and NO

				during reperfusion, 670nm, 14J seconds	and having cardioprotective effects.
Oron Uri et al[88]	2000	50 dogs and 26 rats	Scar tissue formation after MI	Trans thoracic laser for rats and over epicardial surface in dogs; 803nm, 1.08 J for 3 minutes post MI	LELI after chronic MI reduces (52%) infarction size in LI dogs and reduce dense collagen. After 48 hour of occlusion, Troponin T was 7.5±1.6 U in LI group while 12.0±2.6U in NLI group.
Quirk Brendan J. et al[89]	2014	75 rats (18 invitro and 57 invivo)	Protection against ischemia-reperfusion injury	Myocardium LED; 670nm, 26J/cm^2 3 minutes before reperfusion and continuing 7 minutes after reperfusion	Reduce infacrtion size and Troponin I in invivo model. Infarction size (% of area of LV) in control vs. NIR is: for 10 min 10.4±4.7 vs. 2.4±1.6, for 15 min 26.8±9.7 vs. 16.2±6.2, for 20 min 54.7±4.4 vs. 35.4±2.8 and for 30 min 62.0±1.1 vs. 37.1±7.0.

Tuby Hana et al[90]	2011	72 rats randomized in 3 groups	Cardioprotective effect of laser therapy via induction of autologous mesenchymal stem cells	LLLT over myocardium or tibia, 804nm, 1J for 100 seconds Post MI	Reduce scarring and infarction size. MI size was 35±2% in control group while 24±1% in LLLT over myocardium while 8.4±0.8% in LLLT over tibia group.
Yaakobi Tali et al[91]	2020	65 rats	Long term effect of LELI on myocardial infarction and reperfusion injury	Trans thoracic laser; 804nm, 0.27 J for 1 minute post MI and for 3 minutes on 3rd day post MI	Reduction in necrotic scarred tissue. After 14, 21 and 45 days of ligation Infarction size in NLI group was 52±12, 47±11 and 34±7% while in LI group it was 20±8, 15±6 and 10±4% respectively.
Yang Zhikai et al[92]	2011	94 rats	Cardiac cytokines post AMI	Myocardium laser; 635nm, 1J/cm^2 for 150seconds after reperfusion	Reduced infarction size (37.0±5.6% in LI group while 42.4±5.0% in control group), no change in heart functions (49.14±6.93% in control group

					while 81.45±4.66% in sham group) and increase cardiac cytokines.
Tuby Hana et al[93]	2006	147 rats	Effect of LLLT on VEGF and iNOS	Myocardium and trans thoracic laser; 804nm, 0.96J/cm^2 and 0.6 J/cm^2, 1.44 J/cm^2, 2.04 J/cm^2 for 2 minutes pre and post condition	Increase VEGF at 24 - 48 hours, angiogenesis and iNOS.
Yang Jitao et al[94]	2013	120 rats	Effect of LLLT on oxygen free radicals and ventricular remodeling post MI	Myocardium laser, 635nm, 0.96 J/cm^2 for 125 seconds after 3 weeks of MI	LLLT reduces oxygen free radicals & infarction size (18±9 % in LLLI group while 35±10% in control group) , attenuate the collagen fiber formation and increased ventricular wall thickness
Blatt Alax et al[80]	2016	Pigs	Scarring and heart function post MI	LLLT over tibia; 808nm, 1J/cm^2 for 100	Significant reduction in scarring

				seconds post MI	(infarction size was 5.2±0.82% in LI group while 16.6±3.7%) and improves angiogenesis & heart functions (LVEF in control group was 64±2 before MI and 42±3, 66±0.5 after 2 hours and 6 weeks of MI while in LI group it was 60±2 before MI and 50±0.7, 77±1.3 after 2 hours and 6 weeks of MI respectively) in acute or long term phase.
Human clinical trials					
Elbaz-Greener Gabby et al[95]	2018	Individuals with STEMI	Difference in door to balloon time, Cardiac enzyme, LVEF	LLLT over tibia (non- invasive to the bone); 808nm, 1J/cm^2 for 100 seconds, pre PCI and post 24 hours and 3	No difference in door to balloon time (41±8 min in LLLT vs 41±1 min in NLT group), reduce Troponin T (2.7±1.4ng/ml in

				days of PCI	LLLT vs 5.2±1.8ng/ml)
Fernandes Gilderlene Alves et al[81]	2016	Individuals (n=24) who underwent CABG	Healing effect of sternotomy incision	Over 8 spots along the incision by direct contact method; 660nm, 6 J/cm^2 for 60 seconds at each spots immediately after surgery and on alternate day till POD8.	LLLT reduces hyperemia, incisional bleeding and dehiscence.
Khoo Nooshafarin Kazemi et al[79]	2014	Individuals (n=60) who underwent CABG	Cardiac tissue healing markers (CPK, CPK-MB, LDH)	Over the incision and pericardium in left parasternal area (2nd, 3rd intercostal space and apex); 810nm, 6J/cm^2 immediate after surgery and subsequent 2 days	Statistical significant difference in the CPK, CPK-MB and LDH in laser group.
Derkacz Arkadiusz et al[96]	2010	Individuals (n=101) who underwent PCI	MACE, restenosis	Intravascular LPLI; 808nm, 9J/cm^2	Reduces rate of MACE (at 6 & 12 month 7.7% in Laser group while

					in control group 14.3% at 6 month & 18.4% at 12 month) and significant difference in minimal lumen diameter, late lumen loss and late lumen loss index
Karlekar Anil et al[30]	2015	Individuals (n=100) underwent CABG	Pain (VRS)	Class IV laser therapy over the incision via non-contact method	Significantly reduces the pain, can be an effective component of MMA

3. Methodology

3.1 Study design: Pre Test- Post Test Randomized Sham Controlled trial.

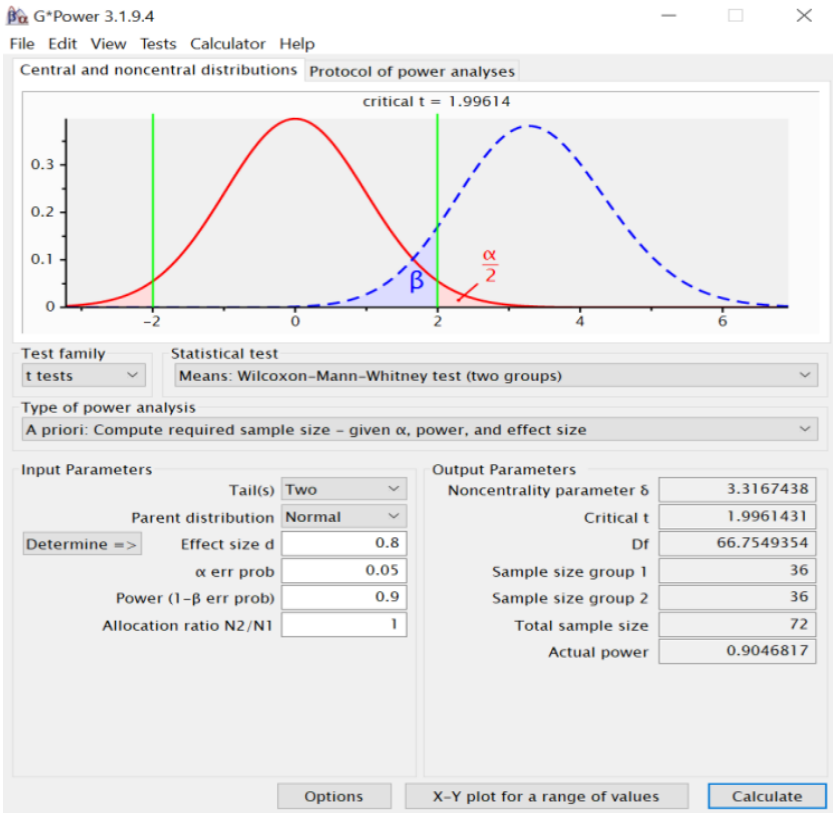
3.2 Study location: Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Mullana, Ambala, Haryana- INDIA.

3.3 Study Setting: Cardiac Care Unit (CCU), Maharishi Markandeshwar Institute of Medical Sciences & Research and Cardiopulmonary Physiotherapy Research Lab, Maharishi Markandeshwar Institute of Physiotherapy & Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana- INDIA.

3.4 Sample design: Purposive sampling

3.4 Randomization: Block Randomization

3.5 Sample size: Sample size was calculated by using G power software, version 3.1.9.4 (Heinrich Heine University Dusseldorf, North Rhine-Westphalia; Germany) with effect size 0.8 and power of the study 90%. Minimum sample size required is 72 (36 in each group). We planned to recruit a total sample size of 80, 40 individuals in each group including 10% dropout rate.



3.6 Selection Criteria

3.6.1 Inclusion criteria

1. Individuals with STEMI type of Acute Coronary Syndrome (ACS) who underwent angioplasty with drug eluting implantation
2. Both male and female above 18 years of age
3. Hemodynamically stable
4. Who voluntarily signed the informed consent

3.6.2 Exclusion Criteria

1. Tumor or growth around mediastinum
2. Temporary or permanent pacemaker
3. Receiving steroids or photosensitive drugs

4. Pregnancy
5. Epilepsy
6. Abnormal liver function test
7. LVEF ≤ 30%

3.7 Variable

3.7.1 Independent variable

1. Class IV Laser

3.7.2 Dependent variable

1. Troponin –I
2. Left ventricular ejection fraction
3. Seattle angina questionnaire

3.8 Material used

1. Seattle angina Questionnaire
2. Echocardiography
3. Lab test for Cardiac Biomarker.
4. Electrocardiogram

3.9 Outcome Measures

3.9.1 Primary Outcome Measures

1. Cardiac Biomarkers (Troponin I)
2. Left ventricular Ejection fraction
3. Seattle angina Questionnaire

Procedure

The study protocol is approved by the departmental research committee of MMIPR on August 10, 2021. After getting the approval of Institutional Research Ethics Committee, the individuals admitted in the Cardiac Care Unit of MMIMSR, Mullana, Ambala, Haryana during the study period will be screened according to selection criteria. Then the invited participants will be asked to sign a written informed consent for their voluntarily participation in the study. Participants will be divided into two group of equal size (n = 40): Sham control group and experimental group by block randomization.

Block randomization procedure will be conducted manually by drawing 80 blocks (20 rows with 4 blocks in each row). The primary investigator is a more than five year experienced cardiorespiratory therapist who provide laser irradiation and the cardiologist who perform echocardiography, the lab technician who assess cardio biomarker will be blinded. The participants will also be blinded to the study by use of laser protected eye wears.

A pre interventional assessment consists of demographic details, inclusion and exclusion criteria certification, an explanation of the procedures, clinical assessment including base line assessment of outcome measures.

1. Cardiac Biomarkers (Troponin – I) will be assessed by lab investigations.

   A biomarker that is highly sensitive or specific, release early after myocardial injury and helps to make diagnosis should be considered as ideal biomarker. Troponin T and I can be used as an early marker as it is more sensitive. Recently, Troponin is the best marker for definitive diagnosis of acute myocardial injury.[60]

   Normal reference range of troponin I: 0.04ng/ml [97]

2. Left ventricular Ejection fraction will be assessed by Echocardiography.

   Left ventricular ejection fraction is a direct indicator of left ventricle systolic function. Normal range of EF as per the European Association of Cardiovascular imaging and American society of Echocardiography is 52%-72% and 50%-70% as per the American college of Cardiology, and less than 30% is labeled as severe dysfunction.[98]

3. Functional status will be assessed by Hindi version of Seattle angina Questionnaire.

   Functional status of an individual with ACS will be assessed in the five domains i.e. physical limitation, angina frequency, angina stability, treatment satisfaction and Quality of life. NO summary score of SAQ is generated because, the each of 5 domains are assessed on an individual ordinal scale which scored a unique dimension of the disease.[63] Score of SAQ categorized as 0 to 50 = poor to fair, 50 to 75 = good and 75 to 100 for physical limitation, quality of life and summery score, while 0 to 60 represent daily to weekly angina, 60 to less than 100 monthly angina and 100 no angina for the angina frequency.[99]

After assessing the baseline outcome measures, the experimental group will be irradiated with Class IV laser for three days; immediately (within 30 minutes) after the angioplasty and subsequent two days. The irradiation will be given at three spot(s) over the pericardium (left sternal border to mid clavicular line in the 2^{nd}, 3^{rd} intercostal space and over the apex) [10] for a duration of 60 seconds at each point as shown in figure 2. During the irradiation phase, the probe will be placed perpendicularly and in direct contact with the skin. ECG rhythm and other vitals will be keenly observed during the entire period of irradiation. Both the patient and laser giver will use the laser protected eye wears to ensure standard practice for the laser. On the other hand, the same class IV laser probe will be placed over the same spots in the sham control group but

the laser energy will not be delivered. The details of the instruments used for irradiation are given in table below:

Table 3.1: Parameters of class IV laser to be used in this study

Parameter	Value
Equipment	LCT-1000C (LiteCure Medical)
Treatment laser wavelength	980nm
Frequency	2500 Hz
Power	6W
Energy density	$6J/cm^2$
Time	60 seconds (each spot area)
Total energy per point	360 J
Spot	3
Application mode	Direct contact with skin at 90^0 and slowly moving the probe

All the outcome measures will be reassessed on the 3rd day post intervention, in between the cardiac biomarkers (Troponin I) will be assessed during peak hours (after 10 hour of PCI).

After the completion of data collection for both the group, the Pre-test and post test score of outcome measures, basic demographical details will be summarized descriptively. The Statistical Package of Social Sciences (SPSS) version 20 will be used for analysis. Analysis will be done for all the participants of the study. Normality of the data will be assessed by Kolmogorov-Smirnov test. If the data will be normally distributed the descriptive statistics will be expressed as mean±SD and 95% confidential interval. Paired t test will be used for within group comparison and unpaired t test for between the group comparison or if the data will not be normally distributed the descriptive statistics will be expressed as median (interquartile range) with range then Mann-Whitney U test for within the group analysis and Wilcoxon signed rank

test for between the group analysis. Statistical significance will be set at $p<0.05$ to minimize type 1 error. Post hoc power analysis will be performed using G power to verify whether the study attained sufficient power or not.

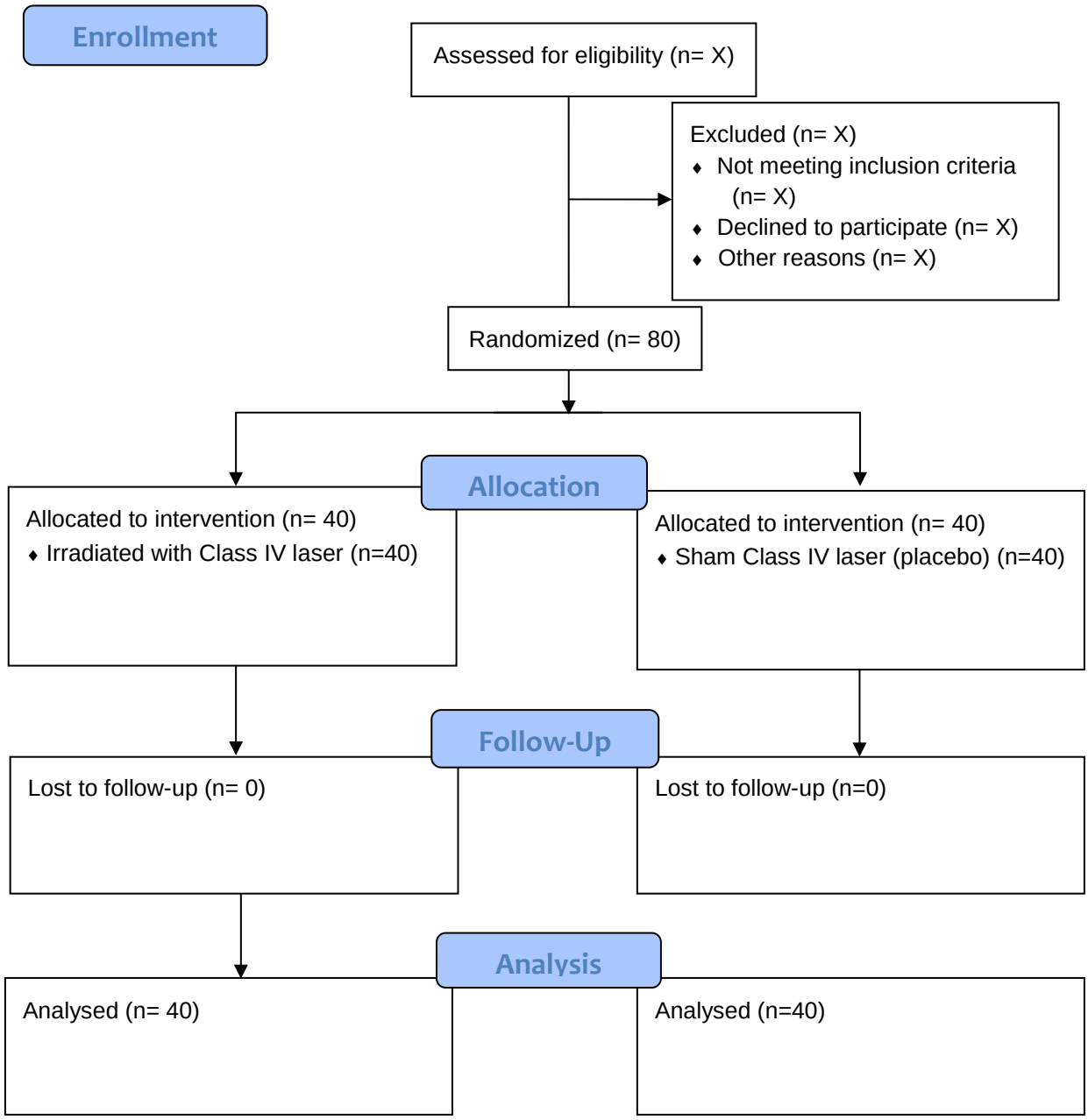


Figure 3.1: Flow Diagram of the study

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-allocation (treatment)**			**Follow-up (evaluations)**	
TIMEPOINT**	***Day 1***	**Day 1**	***Day 1 (Within 30 minutes after angioplasty)***	***Day 2***	***Day 3***	***10 hour post angioplasty***	***Day 3***
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
Allocation		X					
INTERVENTIONS:							
Group A: Experimental			X	X	X		
Group B: Sham Control			X	X	X		
ASSESSMENTS:							
Troponin I		X				X	X
Ejection Fraction		X					X
Seattle angina Questionnaire		X					X

Figure 3.2: Schedule of enrollment, intervention and assessment

4. Discussion

In this study, we intend to determine the efficacy of Class IV Laser therapy in improving ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome. The results of this study may indicate that the class IV laser therapy has beneficial effects on left ventricular ejection fraction, cardiac biomarkers and functional outcomes among the individuals with acute coronary syndrome who underwent coronary angioplasty. Class IV laser therapy is already proven effective in treating postoperative pain in off-pump CABG patients and recommended as a component of multi-model analgesia. The beneficial effect of class IV laser therapy may be due to its anti-inflammatory effect, improvement of microcirculation, cardioprotective effects which help in reduction of myocardial infarction size, prevention of myocardial reperfusion injury, which is already being proven in published literature with low level laser. Most of the studies were conducted among the animal model and in-vitro with low level laser therapy. In a human trial, the low level laser therapy after CABG is found to be effective in reduction in cardiac cellular damage and enhancing the tissue repair.[79] Post STEMI, LLLT to bone marrow is also effective to improve Troponin level without any delay in door to balloon time.[95]

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Plagiarism Report

URKUND

Urkund Analysis Result

Analysed Document:	Mandeep_PhD Synopsis.doc (D111699765)
Submitted:	8/26/2021 11:32:00 AM
Submitted By:	asirjohnsamuel@mmumullana.org
Significance:	3 %

Sources included in the report:

https://worldwidescience.org/topicpages/a/acute%2Bnon-st-elevation%2Bmyocardial.html
https://www.researchgate.net/publication/26864153_Acute_Coronary_Syndromes_Diagnosis_and_Management_Part_I
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2755812/
https://www.openaccessjournals.com/articles/an-overview-of-managing-patients-with-coronary-heart-and-its-pathogenesis-antiplatelet-andor-anticoagulation-therapy-for.pdf
https://www.slideshare.net/deeevardone/acute-coronary-syndrome-52492566

Instances where selected sources appear:

8

Informed Consent form (WHO-format)

Informed consent form (ICF)

This Informed Consent Form is for individuals who admitted in MMIMSR-Mullana with a diagnosis of ACS and underwent angioplasty and who we are inviting to participate in this research. The title of our research project is "Class IV Laser therapy on Ejection fraction, Cardiac biomarkers and Functional outcomes among individuals with Acute Coronary Syndrome"

Name of Principal Investigator: Mandeep Kumar Jangra

Name of Organization: MMIPR.

Name of Sponsor: Nil.

This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form.

Information sheet

I Mandeep Kumar Jangra, a student of Doctor of Philosophy (Physiotherapy) in Maharishi Markandeshwar Institute of Physiotherapy & Rehabilitation, Mullana-Ambala. We are doing a research to determine the efficacy of class IV laser therapy in improving ejection fraction, cardiac biomarkers and functional outcomes among individuals with acute coronary syndrome. I will give you all the detailed information about our research and invite you to participate in our research project. You can take your own time to think whether you will participate or not and you can talk to anyone you feel comfortable about the research.

There may be some medical terms that you do not understand. Please ask me to stop and explain those terms. If you have questions later about this research, you can ask me or any supporting staffs associated with this study.

Purpose of the Research

ACS is a major health issue which reaches epidemic proportion and is a single and foremost cause of deaths and Disability Adjusted Life Years (DALYs) which accounts for approximately 7 million deaths and 129 million DALYs annually. According to Global Burden of Disease study, Overall death rate due to CVD (272/100000) in India is higher than the global (235/100000). The revascularization of the occluded coronary artery is the utmost to treat this, but revascularization also lead to myocardial reperfusion injury. So there is definite need to explore an effective conservative management tool to limit reperfusion injury and improve the clinical outcomes in individuals with acute coronary syndrome.

Type of Research Intervention:

In this research, after your angioplasty you are supposed to be irradiated with class IV laser at the 3 places over the pericardial region for 60 second at each place.

Participant selection:

We are inviting all the individuals with ACS who under angioplasty at MMIMSR-Mullana to participate in this research.

Prior to your participation, an investigator will take your brief medical history to determine your disease and problem, which would make you eligible to participate. You will be asked to provide general information about yourself like age and a few general parameters which will also be recorded. You will be assigned a subject number so that your name will not be associated with any of the findings of the study.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. If you don't want to participate in this research you will be offered the treatment routinely offered in this hospital for Acute Coronary Syndrome. You may change your mind later and withdraw your participation from the study at any time even if you agreed earlier.

Procedure and protocol:

Because we don't know that Class IV laser along with the angioplasty is better than the angioplasty alone in improving cardiac functions among individuals with ACS. To determine this, we will put the participants into two groups by block randomization.

Participants in one group will be given the standardized treatment protocol with Class IV laser (Sham) while participants in other group will irradiate with Class IV laser along with standardized protocol. It is important that neither you nor the assessor know in which group you are. This is the best way we have for testing without being influenced by what we think or hope

might happen. We will then compare which of the two have best results. The healthcare providers will be looking after you and the other participants very carefully during the study. If the assessor is concerned about the group in which you are and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researches.

A sham Class IV laser is the same laser modality but we keep it turned off. For the research to be good, it is important that you do not know whether you have been given the real treatment or the pretend. This is the best way we have for knowing what the intervention we are testing really does.

We will take blood from your arm using a syringe and needle. Each time we will take about 5 ml blood at day 1 after angioplasty and at day 3 after the intervention. Echocardiography will be done at day 1 and day 3 after intervention.

Description of the process:

During the research you have to remain admitted for 3 days.

- At day 1, after the angioplasty a small amount of blood (approx. 5ml) will be taken from your arm with a syringe. This blood will be tested for Cardiac Biomarker (Troponin-I). Echocardiography will be performed to assess the LVEF and size of myocardial infarction. One self-administered questionnaire will be provided to you to assess the functional outcomes.
- After 3 days, the same investigations will be repeated.

Duration:

The research will take place over 3 days.

Side effects:

Usually, there are no any side effects of the class IV laser. If you are photosensitive or on photosensitive drugs then you are excluded from the study. However, we will follow you closely and keep track of any unwanted effects or any problem.

Risk:

In few cases due to high power or energy density localised skin burn may occur, if such happens we will discontinue the irradiation while the possibility of any risk is very low, you should still be aware of the possibility. We will try to decrease the chances of such event occurring, but if something unexpected happens, we will provide you with relevant solution.

Benefits:

If you participate in this research, you will provided the intervention (Class IV laser) at free of cost. Class IV laser is supposed to beneficial in reducing myocardial reperfusion injury and improve heart function and functional outcomes.

Reimbursements:

You will not be given any other money or gifts to take part in this research.

Confedentiality:

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone. Photographs or video maybe obtained during research. These photographs or video may be used for research/education purpose only after hiding your identity by masking your face.

Sharing the result:

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw:

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Alternatives to Participating

If you don't want to participate in this research you will be offered the treatment routinely offered in this hospital for Acute Coronary Syndrome.

Who to contact:

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Mandeep K Jangra

Department of Physiotherapy,

MMIPR, Maharishi Markandeshwar (Deemed to be University),

Mullana-Ambala (Haryama), India.

Email: mandeep.jangra@mmumullana.org

Ph No.: +919416797708

Prof. (Dr.) Asir John Samuel, PhD

MMIPR, Maharishi Markandeshwar (Deemed to be University),

Mullana-Ambala (Haryama), India.

Email: asirjohnsamuel@mmumullana.org

Ph No.: +918059930222

Prof. (Dr.) Anupam Bhambhani, DM (Cardiology)

MMIMSR, Maharishi Markandeshwar (Deemed to be University),

Mullana-Ambala (Haryama), India

Email: anupam.bhambhani@yahoo.in

Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant _____

Signature of Participant _____

Date _____

Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Participants of this will be irradiated with Class IV laser therapy followed by standard treatment regime.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

सूचित सहमति प्रपत्र (WHO-प्रारूप)

परिशिष्ट 1

सूचित सहमति फॉर्म (आईसीएफ)

यह सूचित सहमति प्रपत्र उन व्यक्तियों के लिए है जो एमएमआईएमएसआर-मुल्लाना में एसीएस के निदान के साथ भर्ती हुए हैं और एंजियोप्लास्टी कर चुके हैं और जिन्हें हम इस शोध में भाग लेने के लिए आमंत्रित कर रहे हैं। हमारी शोध परियोजना का शीर्षक है "एक्यूट कोरोनरी सिंड्रोम वाले व्यक्तियों के बीच इजेक्शन अंश, कार्डिएक बायोमार्कर और कार्यात्मक परिणामों पर चतुर्थ श्रेणी लेजर थेरेपी"

प्रधान अन्वेषक का नाम: मनदीप कुमार जांगड़ा

संगठन का नाम: एमएमआईपीआर

प्रायोजक का नाम: शून्य।

इस सूचित सहमति फॉर्म के दो भाग हैं:

• सूचना पत्रक (आपके साथ शोध के बारे में जानकारी साझा करने के लिए)

• सहमति का प्रमाण पत्र (हस्ताक्षर के लिए यदि आप भाग लेने के लिए सहमत हैं)

आपको पूर्ण सूचित सहमति फॉर्म की एक प्रति दी जाएगी।

सूचना पत्रक

मैं मनदीप कुमार जांगड़ा, महर्षि मार्कंडेश्वर इंस्टीट्यूट ऑफ फिजियोथेरेपी एंड रिहैबिलिटेशन, मुलाना-अंबाला में डॉक्टर ऑफ फिलॉसफी (फिजियोथेरेपी) का छात्र हूं। हम तीव्र कोरोनरी सिंड्रोम वाले व्यक्तियों के बीच इजेक्शन अंश, कार्डियक बायोमार्कर और कार्यात्मक परिणामों में सुधार के लिए चतुर्थ श्रेणी लेजर थेरेपी की प्रभावकारिता निर्धारित करने के लिए एक शोध कर रहे हैं। मैं आपको हमारे शोध के बारे में सभी विस्तृत जानकारी दूंगा और आपको हमारी शोध परियोजना में भाग लेने के लिए आमंत्रित करूंगा। आप यह सोचने के लिए अपना समय ले सकते हैं कि आप भाग लेंगे या नहीं और आप किसी से भी बात कर सकते हैं जिसे आप शोध के बारे में सहज महसूस करते हैं।

कुछ चिकित्सीय शब्द हो सकते हैं जिन्हें आप नहीं समझते हैं। कृपया मुझे उन शर्तों को रोकने और समझाने के लिए कहें। यदि इस शोध के बारे में बाद में आपके कोई प्रश्न हैं, तो आप मुझसे या इस अध्ययन से जुड़े किसी भी सहायक कर्मचारी से पूछ सकते हैं।

अनुसंधान का उद्देश्य

एसीएस एक प्रमुख स्वास्थ्य समस्या है जो महामारी के अनुपात तक पहुंचती है और मृत्यु और विकलांगता समायोजित जीवन वर्ष (डीएएलवाई) का एकमात्र और प्रमुख कारण है, जिसमें सालाना लगभग 7 मिलियन मौतें और 129 मिलियन डीएएलवाई होते हैं। ग्लोबल बर्डन ऑफ डिजीज अध्ययन के अनुसार, भारत में सीवीडी (272/100000) के कारण समग्र मृत्यु दर वैश्विक (235/100000) से अधिक है। अवरुद्ध कोरोनरी धमनी का पुनरोद्धार इसका इलाज करने के लिए सबसे अधिक है, लेकिन पुनरोद्धार भी मायोकार्डियल रीपरफ्यूजन चोट का कारण बनता है। इसलिए रीपरफ्यूजन की चोट को सीमित करने और तीव्र कोरोनरी

सिंड्रोम वाले व्यक्तियों में नैदानिक परिणामों में सुधार करने के लिए एक प्रभावी रूढ़िवादी प्रबंधन उपकरण का पता लगाने की निश्चित आवश्यकता है।

अनुसंधान हस्तक्षेप का प्रकार:

इस शोध में, आपकी एंजियोप्लास्टी के बाद, आपको पेरीकार्डियल क्षेत्र के 3 स्थानों पर प्रत्येक स्थान पर 60 सेकंड के लिए चतुर्थ श्रेणी के लेजर से विकिरणित किया जाना चाहिए।

प्रतिभागी चयन:

हम एसीएस वाले सभी व्यक्तियों को आमंत्रित कर रहे हैं जो इस शोध में भाग लेने के लिए एमएमआईएमएसआर-मुल्लाना में एंजियोप्लास्टी कर रहे हैं।

आपकी भागीदारी से पहले, एक अन्वेषक आपकी बीमारी और समस्या का निर्धारण करने के लिए आपका संक्षिप्त चिकित्सा इतिहास लेगा, जो आपको भाग लेने के योग्य बनाएगा। आपको अपने बारे में सामान्य जानकारी जैसे उम्र और कुछ सामान्य पैरामीटर प्रदान करने के लिए कहा जाएगा जिसे भी दर्ज किया जाएगा। आपको एक विषय संख्या दी जाएगी ताकि आपका नाम अध्ययन के किसी भी निष्कर्ष के साथ संबद्ध न हो।

इस शोध में आपकी भागीदारी पूर्णतः स्वैच्छिक है। यह आपकी मर्जी है कि भाग लेना है या नहीं। आप भाग लेना चाहते हैं या नहीं, इस अस्पताल में आपको मिलने वाली सभी सेवाएं जारी रहेंगी और कुछ भी नहीं बदलेगा। यदि आप इस शोध में भाग नहीं लेना चाहते हैं तो आपको इस अस्पताल में एक्यूट कोरोनरी सिंड्रोम के लिए नियमित रूप से दिए जाने वाले उपचार की पेशकश की जाएगी। आप बाद में अपना विचार बदल सकते हैं और किसी भी समय अध्ययन से अपनी भागीदारी वापस ले सकते हैं, भले ही आप पहले सहमत हों।

प्रक्रिया और प्रोटोकॉल:

क्योंकि हम नहीं जानते कि एसीएस वाले व्यक्तियों में हृदय संबंधी कार्यों में सुधार के लिए एंजियोप्लास्टी के साथ चतुर्थ श्रेणी का लेजर केवल एंजियोप्लास्टी से बेहतर है। इसे निर्धारित करने के लिए, हम प्रतिभागियों को ब्लॉक रैंडमाइजेशन द्वारा दो समूहों में रखेंगे।

एक समूह के प्रतिभागियों को चतुर्थ श्रेणी के लेजर (शाम) के साथ मानकीकृत उपचार प्रोटोकॉल दिया जाएगा, जबकि दूसरे समूह के प्रतिभागियों को मानकीकृत प्रोटोकॉल के साथ चतुर्थ श्रेणी के लेजर से विकिरणित किया जाएगा। यह महत्वपूर्ण है कि न तो आप और न ही मूल्यांकनकर्ता को पता हो कि आप किस समूह में हैं। हम जो सोचते हैं या आशा करते हैं उससे प्रभावित हुए बिना परीक्षण के लिए हमारे पास यह सबसे अच्छा तरीका है। फिर हम तुलना करेंगे कि दोनों में से किसके सर्वोत्तम परिणाम हैं। अध्ययन के दौरान स्वास्थ्य सेवा प्रदाता आपकी और अन्य प्रतिभागियों की बहुत सावधानी से देखभाल करेंगे। यदि मूल्यांकनकर्ता उस समूह के बारे में चिंतित है जिसमें आप हैं और परिवर्तन करें। यदि कोई ऐसी बात है जिसके बारे में आप चिंतित हैं या जो आपको शोध के बारे में परेशान कर रही है तो कृपया मुझसे या किसी अन्य शोध से बात करें।

एक दिखावा क्लास IV लेज़र वही लेज़र मोडेलिटी है लेकिन हम इसे बंद रखते हैं। शोध के अच्छे होने के लिए यह जरूरी है कि आपको पता न चले कि आपको असली इलाज दिया गया है या दिखावा। हमारे पास यह जानने का सबसे अच्छा तरीका है कि हम जिस हस्तक्षेप का परीक्षण कर रहे हैं वह वास्तव में क्या करता है।

हम एक सिरिंज और सुई का उपयोग करके आपकी बांह से खून लेंगे। हर बार हम एंजियोप्लास्टी के बाद 1 दिन में और हस्तक्षेप के 3 दिन बाद लगभग 5 मिलीलीटर रक्त लेंगे। इकोकार्डियोग्राफी हस्तक्षेप के बाद पहले दिन और तीसरे दिन की जाएगी।

प्रक्रिया का विवरण:

रिसर्च के दौरान आपको 3 दिन तक भर्ती रहना होता है।

- पहले दिन, एंजियोप्लास्टी के बाद एक सिरिंज से आपकी बांह से थोड़ी मात्रा में रक्त (लगभग 5 मिली) लिया जाएगा। कार्डिएक बायोमार्कर (Troponin-I) के लिए इस रक्त का परीक्षण किया जाएगा। एलवीईएफ और मायोकार्डियल इंफार्क्शन के आकार का आकलन करने के लिए इकोकार्डियोग्राफी की जाएगी। कार्यात्मक परिणामों का आकलन करने के लिए आपको एक स्व-प्रशासित प्रश्नावली प्रदान की जाएगी।
- 3 दिनों के बाद, वही जाँच दोहराई जाएगी।

अवधि:

शोध तीन दिनों तक चलेगा।

दुष्प्रभाव:

आमतौर पर, चतुर्थ श्रेणी के लेजर का कोई दुष्प्रभाव नहीं होता है। यदि आप प्रकाश संवेदनशील हैं या प्रकाश संश्लेषक औषधियों का सेवन कर रहे हैं तो आपको अध्ययन से बाहर रखा गया है। हालाँकि, हम आपका बारीकी से अनुसरण करेंगे और किसी भी अवांछित प्रभाव या किसी समस्या पर नज़र रखेंगे।

जोखिम:

कुछ मामलों में उच्च शक्ति या ऊर्जा घनत्व के कारण स्थानीयकृत त्वचा जल सकती है, यदि ऐसा होता है तो हम विकिरण को बंद कर देंगे, जबकि किसी भी जोखिम की संभावना बहुत कम है, फिर भी आपको संभावना के बारे में पता होना चाहिए। हम ऐसी घटना होने की संभावना को कम करने की कोशिश करेंगे, लेकिन अगर कुछ अप्रत्याशित होता है, तो हम आपको प्रासंगिक समाधान प्रदान करेंगे।

लाभ:

यदि आप इस शोध में भाग लेते हैं, तो आपको नि:शुल्क हस्तक्षेप (चतुर्थ श्रेणी का लेजर) प्रदान किया जाएगा। चतुर्थ श्रेणी के लेजर को मायोकार्डियल रीपरफ्यूजन की चोट को कम करने और हृदय समारोह और कार्यात्मक परिणामों में सुधार करने के लिए फायदेमंद माना जाता है।

प्रतिपूर्ति:

इस शोध में भाग लेने के लिए आपको कोई अन्य धन या उपहार नहीं दिया जाएगा।

गोपनीयता:

इस शोध परियोजना से हम जो जानकारी एकत्र करते हैं उसे गोपनीय रखा जाएगा। आपके बारे में जो जानकारी शोध के दौरान एकत्र की जाएगी उसे हटा दिया जाएगा और इसे कोई और नहीं बल्कि शोधकर्ता देख पाएंगे। आपके बारे में किसी भी जानकारी पर आपके नाम की जगह एक नंबर होगा। केवल शोधकर्ताओं को ही पता चलेगा कि आपका नंबर क्या है और हम उस जानकारी को एक ताला और चाबी से बंद कर देंगे। इसे किसी के साथ साझा या दिया नहीं जाएगा। शोध के दौरान प्राप्त फोटो या वीडियो। इन तस्वीरों या वीडियो का उपयोग अनुसंधान/शिक्षा के उद्देश्य के लिए आपका चेहरा छुपाकर, और आपकी पहचान छुपाने के बाद किया जा सकता है।

परिणाम साझा करना:

इस शोध को करने से हमें जो ज्ञान प्राप्त होता है, उसे जनता के लिए व्यापक रूप से उपलब्ध कराने से पहले सामुदायिक बैठकों के माध्यम से आपके साथ साझा किया जाएगा। गोपनीय जानकारी साझा नहीं की जाएगी। समुदाय में छोटी-छोटी बैठकें होंगी और इनकी घोषणा की जाएगी। इन बैठकों के बाद, हम परिणाम प्रकाशित करेंगे ताकि अन्य इच्छुक लोग हमारे शोध से सीख सकें।

मना करने या वापस लेने का अधिकार:

यदि आप ऐसा नहीं करना चाहते हैं तो आपको इस शोध में भाग लेने की आवश्यकता नहीं है। आप अपने द्वारा चुने गए किसी भी समय शोध में भाग लेना बंद भी कर सकते हैं। यह आपकी पसंद है और आपके सभी अधिकारों का सम्मान किया जाएगा।

भाग लेने के विकल्प

यदि आप इस शोध में भाग नहीं लेना चाहते हैं तो आपको इस अस्पताल में एक्यूट कोरोनरी सिंड्रोम के लिए नियमित रूप से दिए जाने वाले उपचार की पेशकश की जाएगी।

किससे संपर्क करें:

यदि आपके कोई प्रश्न हैं, तो आप उनसे अभी या बाद में, अध्ययन शुरू होने के बाद भी पूछ सकते हैं। यदि आप बाद में प्रश्न पूछना चाहते हैं, तो आप निम्न में से किसी से भी संपर्क कर सकते हैं:

1. मनदीप कुमार जांगड़ा

   फिजियोथेरेपी विभाग,

   एमएमआईपीआर, महर्षि मार्कंडेश्वर (डीम्ड टू बी यूनिवर्सिटी),

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   ईमेल: mandeep.jangra@mmumullana.org

   फोन नंबर: +919416797708

2. (आचार्य) डॉ असीर जॉन सैमुअल, पीएचडी

   एमएमआईपीआर, महर्षि मार्कंडेश्वर (डीम्ड टू बी यूनिवर्सिटी),

   मुलाना-अंबाला (हरियाणा), भारत

फोन नंबर: 8059930222

3. (आचार्य) डॉ अनुपम भंभानी, डीएम (कार्डियोलॉजी)

MMIMSR, महर्षि मार्कंडेश्वर (डीम्ड टू बी यूनिवर्सिटी),

मुलाना-अंबाला (हरियाणा), भारत

ईमेल: anupam.bhanmbhani.yahoo.in

सहमति का प्रमाण पत्र

मैंने पूर्वगामी जानकारी पढ़ी है, या यह मुझे पढ़ी गई है। मुझे इसके बारे में प्रश्न पूछने का अवसर मिला है और जो भी प्रश्न मैंने पूछे हैं उनका उत्तर मेरी संतुष्टि के लिए दिया गया है। मैं स्वेच्छा से इस शोध में एक भागीदार के रूप में भाग लेने के लिए।

प्रतिभागी का प्रिंट नाम _____

प्रतिभागी का हस्ताक्षर _____

तारीख _____

दिन /महीने/ साल

अगर अनपढ़ है

मैंने संभावित प्रतिभागी को सहमति फॉर्म के सटीक पढ़ने को देखा है, और व्यक्ति को सवाल पूछने का अवसर मिला है। मैं पुष्टि करता हूं कि व्यक्ति ने स्वतंत्र रूप से सहमति दे दी है।

गवाह का प्रिंट नाम _____ और प्रतिभागी का अंगूठा प्रिंट

गवाह के हस्ताक्षर _____

तारीख _____

(दिन /महीने/ साल)

सहमति लेने वाले शोधकर्ता / व्यक्ति का कथन

मैंने संभावित प्रतिभागी को सूचना पत्र को सटीक रूप से पढ़ा है, और मेरी पूरी क्षमता से यह सुनिश्चित हो गया है कि प्रतिभागी समझता है कि निम्नलिखित किया जाएगा:

1. इसके प्रतिभागियों को मानक उपचार व्यवस्था के बाद चतुर्थ श्रेणी की लेजर थेरेपी से विकिरणित किया जाएगा।

मैं पुष्टि करता हूं कि प्रतिभागी को अध्ययन के बारे में प्रश्न पूछने का अवसर दिया गया था, और प्रतिभागी द्वारा पूछे गए सभी प्रश्नों का सही और मेरी सर्वश्रेष्ठ क्षमता पर उत्तर दिया गया है। मैं इस बात की पुष्टि करता हूं कि व्यक्ति को सहमति देने के लिए बाध्य नहीं किया गया है, और सहमति स्वतंत्र रूप से और स्वेच्छा से दी गई है।

इस ICF की एक प्रति प्रतिभागी को प्रदान की गई है।

सहमति लेने वाले शोधकर्ता / व्यक्ति का नाम _____

सहमति लेने वाले शोधकर्ता / व्यक्ति का हस्ताक्षर _____

तारीख _____

(दिन /महीने/ साल)

Data Collection Form

Subject Name / No. :

Age:

Gender:

Address:

Occupation:

Marital Status:

Height (cm):

Weight (kg):

Diagnosis:

Date of admission:

Date of assessment:

Variable	**Pre Intervention Score**	**10 hours post angioplasty**	**Post Intervention Score**
Ejection Fraction (%)		NA	
Troponin-I (ng/ml)			
SAQ Score		NA	